REMARKS

This reply is responsive to the final Office Action mailed March 12, 2009 (the "Office Action"). Claims 1–5, 9, 10, 12–14, and 16–22 are pending and under consideration. With this Amendment, new claims 24–39 are added, and claims 9 and 10 are canceled as redundant thereover. Thus, after entry of this Amendment, claims 1–5, 12–14, 16–22 and 24–39 are pending and under consideration. The claims newly added by amendment and the various rejections raised in the Office Action are discussed in more detail, below.

The Amendments to the Claims

New claims 24 – 39 are drawn with particularity to treatment of migraine, and parallel claims 1–5, 12–14, 16–22, drawn to methods of treating disorders of trigeminovascular activation. Support for the new claims can be found in the specification and claims as filed. No new matter has been added.

The Rejections Under 35 U.S.C. § 103

Claims 1–4, 9–10, 12, 13 and 19–22 stand rejected under 35 U.S.C. § 103 as allegedly having been obvious over Pevarello, *et al.* (WO 99/35125, "Pevarello") in view of Strittmatter *et al.*, *Headache* 37:211-216 (1997) ("Strittmatter"). Applicants traverse.

The Office Action correctly characterizes Pevarello as teaching compounds of formula I "used for treating pain." Office Action, p. 3 (emphasis added). More to the point, Pevarello specifically discloses the usefulness of this class of compounds in treating the pain of trigeminal neuralgia; indeed, the Pevarello U.S. national phase counterpart, RE40,259 (of record as IDS citation A34), explicitly claims the treatment of the pain of trigeminal neuralgia using these compounds (see, *e.g.*, claims 33 and 49).

The Office Action correctly notes that Pevarello does not teach the treatment of disorders of trigeminovascular activation. Office Action, p. 4.

To perfect a *prima facie* case of obviousness, the secondary reference must somehow bridge the gap between the prior art treatment of the pain of trigeminal neuralgia and the treatment, presently claimed, of disorders of trigeminovascular activation — Strittmatter (*i*) must provide a motivation to repurpose these known analgesic compounds to treat disorders of trigeminovascular activation, and (*ii*) must provide a reasonable expectation of successfully so doing. The Examiner contends that Strittmatter can satisfy both requirements with a single showing, a demonstration that the treatment of

disorders of trigeminovascular activation is inherent in the prior art methods of treating the pain of trigeminal neuralgia ("by treating trigeminal neuralgia[1] as taught [by] Pevarello, one would in essence be treating a disorder that is trigeminovascularly activated", Office Action at 5).

This is not a fair reading of the reference.

Strittmatter's actual data are quite modest: "we found a significant increase of substance P in the CSF of patients with trigeminal neuralgia." From this observation, based on samples from 16 patients, Strittmatter conjectures that "continuing neurogenic inflammation is an important factor in the pathogenesis of this condition." This conclusion is stated with somewhat greater certainty than seems warranted by 16 lumbar punctures, particularly against an admitted background of uncertainty as to the pathogenesis of this disorder:

> [t]he pathogenesis of trigeminal neuralgia remains unknown. None of the numerous neuroanatomical, neurosurgical, and neuroradiological studies explain the characteristics of the pain in trigeminal neuralgia, such as the sudden onset and the cessation of pain, the separation of the trigger zone from the area of pain, and the absence of sensory loss, even during the refractory period. Although many findings suggest a peripheral cause due to a chronic-intermittent irritation of the trigeminal nerve, some hypotheses involving central concepts such as reverberating circuits, ephaptic connections, and a disturbance of central synaptic activity have been postulated.[2]

To augment the data, and bolster his conclusion that "continuing neurogenic inflammation is an important factor in the pathogenesis" of trigeminal neuralgia, Strittmatter cites to the work of others who purportedly had earlier shown that "[s]ubstance P plays an important role as a pain-inducing excitatory neurotransmitter in neurogenic inflammation, and clinical studies have confirmed this role of substance P as an activator of afferent nociceptive structures in the anatomic region of the trigeminal nerve." Yet it has been established that substance P is a non-specific marker for neurogenic inflammation. *See* Declaration of Giorgio Sandrini, at ¶12. Strittmatter therefore fails to establish that trigeminovascular activation and neurogenic inflammation play a pathogenic role in the pain of trigeminal neuralgia because Strittmatter fails to evaluate markers specific to the disorder. *Id.*, at ¶13.

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1 More properly, by treating ***the pain of*** trigeminal neuralgia.

2 Strittmatter at p. 211.

Assuming, *arguendo*, that in this case, correlation indeed properly equates to causation, and that substance P can properly be assumed to play some role in the *genesis* of trigeminal neuralgia, there is nonetheless no showing that treating the pain of trigeminal neuralgia necessarily and invariably treats a disorder of trigeminovascular activation, as required to demonstrate inherency.

It is true that Strittmatter further states that "recent studies stress the importance of the trigeminovascular system in trigeminal neuralgia," but the cited "studies" – in truth, a single study – does not support the stated proposition. The cited reference "8" is Goadsby *et al.*, "Human *in vivo* evidence for trigeminovascular activation in cluster headache. Neuropeptide changes and effects of acute attacks therapies," *Brain* 117:427-434 (1994) (copy enclosed as Exhibit A); cluster headache is not trigeminal neuralgia. Pointedly, Goadsby states "[d]uring the attacks external jugular vein blood levels of CGRP and VIP were raised while there was no change in neuropeptide Y or substance P." (emphasis added).

Strittmatter does not demonstrate that treatment of the pain of trigeminal neuralgia inherently treats disorders of trigeminovascular activation. It fails, therefore, to provide a motivation to repurpose known analgesic compounds to treat disorders of trigeminovascular activation, and fails to provide a reasonable expectation of successfully so doing. The *prima facie* case of obviousness fails, and the rejection should be withdrawn.

Claims 5 and 16 – 18 are rejected under 35 U.S.C. § 103 as unpatentable over Pevarello in view of Strittmatter, with the additional contention that limitation to three species of compounds within the genus of claim 1, further drawn to the (S) optical isomer, adds no nonobvious subject matter.

The rejection fails for the reasons advanced above with respect to claims 1 – 4, 9 – 10, 12, 13, and 19 – 22: Strittmatter does not motivate the repurposing of applicants' analgesic compounds for treatment of disorders of trigeminovascular activation, nor does it provide any reasonable expectation of so doing. The rejection is further deficient in conflating three different types of "expectation": (*i*) an expectation that the prior art racemates can be resolved into separated optical isomers, (*ii*) an expectation that the resolved isomers will "possess[] substantial[ly] different pharmacological activity," and (*iii*) an expectation that the resolved (S) isomers will have activity in treating disorders of trigeminovascular activation. The last is the legally relevant inquiry here, and the Office Action is wholly silent with respect thereto.

Claim 14 is separately rejected as having been obvious over Pevarello in view of Strittmatter with the observation that the additionally recited dose range is a parameter subject to routine optimization.

With the failure of the secondary reference to establish the rudiments of a *prima facie* case of obviousness, this rejection fails without more.

Claim 23 stands rejected under 35 U.S.C. § 103 over Pevarello in view of Strittmatter, further in view of Goadsby (*Annals of Neurology*, 1993) ("Goadsby").[3]

The rejection is traversed for the reasons advanced above. It is of no moment that Goadsby "teaches that migraines are intimately linked to the trigeminal innervation of the cranial vessels, the trigeminovascular system"; this teaching cannot rectify the deficiency of Strittmatter. Neither of the secondary references, alone or in combination, motivates the use of alpha-aminoamide analgesic compounds, known to be useful in treating the pain of trigeminal neuralgia, in methods of treating migraine, nor do Strittmatter and Goadsby provide a reasonable expectation that these analgesics will be effective in treating migraine disorders. For the same reasons, the rejection would be equally improper if brought against the claims newly added by amendment herein, which are drawn to methods of treating migraine.

Furthermore, a correlation between primary headaches and in particular, migraine and cluster headaches, and the trigeminovascular system would not suggest a correlation exists between the pain of trigeminal neuralgia and the trigeminovascular system. Migraine and trigeminal neuralgia represent distinct disorders with differing clinical presentations, etiologies, epidemiology, and treatment protocols. *See* Declaration of Giorgio Sandrini, at ¶¶2–11 and ¶18. For example, unlike migraine, there is no evidence that sensitization phenomena play a role in the pain of trigeminal neuralgia. *Id.*, at ¶¶16–17. Additionally, in contrast to migraine, the etiology of trigeminal neuralgia, while not well understood, is considered to involve demyelination of nerve fibers and/or compression of blood vessels. *Id.*, at ¶18–21. Because of the differing etiologies of trigeminal neuralgia and migraine, animal models for the conditions are different. *Id.*, at ¶22–24. Further, patients presenting with the disorders are treated differently. *Id.*, at ¶25–30. These differences all suggest that trigeminal neuralgia is <u>not</u> a disorder of trigeminovascular activation.

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[3] Claim 9, drawn to treatment of migraine, was no doubt intended, since claim 23 was canceled prior to the most recent Office Action. Claim 23 had depended directly from claim 1, further limiting the disorder of trigeminovascular activation to migraine; claim 9 as examined is similarly drawn to treatment of migraine.

Conclusion

In view of the foregoing, Applicant submits that all claims are allowable over the citations of record. An indication of allowance of all claims is respectfully solicited. In the event any issues remain, Applicants would appreciate the courtesy of a telephone call to their counsel to resolve such issues and place all claims in condition for allowance.

No fees beyond those due for the extension of time and extra claim fees are believed to be due in connection with this Amendment. However, the Director is authorized to charge any additional fees that may required, or credit any overpayment, to Dechert LLP Deposit Account No. 50-2778 **(Order No. 373987-004US (396982))**.

Respectfully submitted,

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Date: _____

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Stefan M. Miller
Reg. No. 57,623

DECHERT LLP
Customer No. 37509
Tel: 650.813.4800
Fax: 650.813.4848